

Chapter 7

GIT Pharmacology

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Part 1: Peptic Ulcer Disease and Reflux Esophagitis

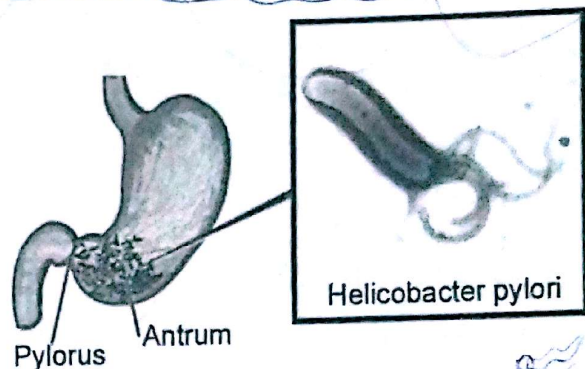
Peptic ulcer

Definition: ulceration of the duodenum or stomach (due to imbalance between local invasive force (e.g. HCl and pepsin) and protective mechanisms).

Invasive factors:

- **Stress:** ↑ HCl and pepsin secretion by parietal cells.
- **Diet:** coffee, alcohol and spices.
- **Bile reflux**
- **Drugs:** NSAIDs, corticosteroids, nicotine, morphine, methylxanthines, reserpine.
- **Infection by *Helicobacter pylori*.**

H. pylori is spiral gram -ve, flagellates found in the antrum of human stomach. Certain enzymes and toxins produced by the bacteria cause tissue damage. Infection with *H. pylori* is diagnosed by endoscopy.

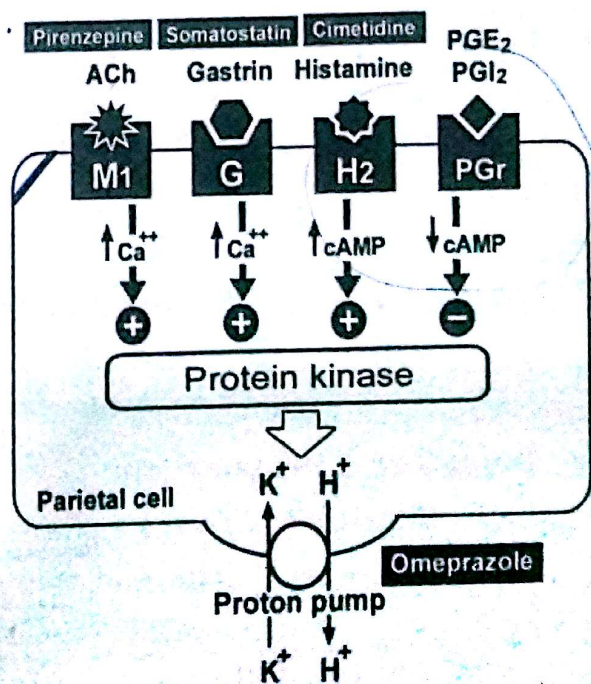


Defensive mechanisms:

- Mucus production by gastric mucosa.
- Local PGE₂ and PGI₂ production.
- Pancreatic bicarbonate secretion.
- Good mucosal blood flow.

Regulation of HCl secretion

- **Ach:** ↑ HCl secretion through M₁ receptors → ↑ intracellular Ca²⁺.
- **Gastrin:** ↑ HCl secretion through G receptors → ↑ intracellular Ca²⁺.
- **Histamine:** ↑ HCl secretion through H₂ receptors → ↑ intracellular cAMP.



Both Ca^{2+} and cAMP activate H^+/K^+ ATPase at the membrane of the parietal cell to secrete H^+ into the gastric lumen "proton pump".

- PGE_2 and PGI_2 : $\downarrow$ HCl secretion (act on PG receptors $\rightarrow$ $\downarrow$ intracellular cAMP).

Clinical picture

- Epigastric pain: characterized by:
 - Diffuse and worsens by food in GU.
 - Localized (point tenderness) and relieved by food in DU.
- Signs of complications e.g. bleeding, perforation, anemia, etc.

Diagnosis

- Endoscopy: visualization of the ulcer.
- * - Radiologic: by barium meal.



Endoscopic views. (a) Duodenal ulcer with inflamed duodenal folds. (b) Benign gastric ulcer

Therapy of peptic ulcer

Non-drug therapy = life style modification

- Rest and Sedation: they improve healing and relief pain of DU.
- Stop Smoking, Spices, alcohol, coffee, and tea: because they $\uparrow$ HCl.
- Avoid Stress: because stress $\uparrow$ HCl.
- Avoid ulcerogenic drugs: e.g. NSAIDs, corticosteroids, methylxanthines.
- Diet:
 - Frequent small meals in DU in order to buffer high acidity.
 - Encourage milk and fats*
 - Avoid Spices and fried food

Pharmacological therapy

- Drugs that neutralize HCl: antacids
- Drugs that $\downarrow$ HCl secretion:
 - ✓ Selective M_1 blockers: pirenzepine, telenzepine.
 - ✓ H_2 blockers: cimetidine, ranitidine, famotidine.
 - * - Proton pump inhibitors: omeprazole, lansoprazole, etc.

H/K ATPase

Drugs that ↑ mucosal defense mechanisms:

- Sucralfate
- Colloid bismuth compounds: e.g. bismuth subcitrate.
- Carbenoxolone
- PGE₁ analogues: misoprostol

Antimicrobial drugs for *H. pylori*: amoxicillin, clarithromycin, etc.

- Adjuvant therapy: Sedatives (diazepam): to ↓ stress and Multivitamins: to enhance healing.

Antacids

- Antacids are weak bases that are taken orally and partially neutralize gastric acid and reduce pepsin activity.
- They are used for symptomatic relief of hyperacidity symptoms and should not be used as long-term treatment.

Sodium bicarbonate	Calcium carbonate	Magnesium and aluminum salts (Mg hydroxide and Aluminium hydroxide)
▪ It can be absorbed systemically leading to salt & water retention, and metabolic alkalosis. ▪ It is contraindicated in hypertension and heart failure. ▪ It has rapid onset and short duration.	▪ Partially absorbed antacid. ▪ Ca²⁺ may act directly to stimulate gastrin secretion leading to acid rebound. ▪ It is contraindicated in hypercalcemia and renal stones.	▪ They are poorly absorbed from GIT and have no systemic effects. ▪ The unabsorbed Mg salts cause osmotic diarrhea; the unabsorbed Al salts cause constipation. ▪ They have slow onset.

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Adverse effects

■ Change in bowel habits: Al^{3+} hydroxide causes constipation, while Mg^{2+} hydroxide cause diarrhea. For this reason, both salts are combined together to manage this problem.

■ Rebound hyperacidity: with Ca^{2+} and NaHCO_3 containing antacids.

■ Cation overload:

✓ Na^+ salts → hypertension and systemic alkalosis.

✓ Ca^{2+} salts → hypercalcemia, renal stones and milk-alkali syndrome?

Milk-alkali syndrome

Patients with PU usually administer large amounts of milk and antacids to relieve symptoms of hyperacidity.

- Excess milk → hypercalcemia.
- Excess antacids → alkalosis (due to continuous wash of HCl).

■ Decrease absorption of other drugs: the metal ion in some preparations can chelate other drugs especially tetracycline, digitalis and iron.

N.B. when iron or tetracycline is prescribed with antacids, we should make 30 min interval between both drugs to avoid chelation with the antacid.

Decrease HCl secretion

1. Selective M_1 blockers

(Pirenzepine - Telenzepine)

Mechanism of action: selectively block gastric M_1 receptors → ↓ basal HCl secretion.

Uses: They have poor efficacy and undesirable side effects. They are used as adjuvant therapy with H_2 blockers.

Side effects: high doses produce atropine-like effects: dry mouth, blurred vision, tachycardia, urine retention.

N.B.

- Atropine itself is not used in the treatment of PU because it is non-selective M blocker and may aggravate esophageal reflux. stop gastric motility
- The selective M_1 blockers are weak inhibitors of HCl secretion and are not replaced by more effective drugs.

2. H₂ blockers:

(Cimetidine - Ranitidine - Famotidine - Nizatidine)

Mechanism and pharmacological effects

- They act as competitive inhibitors of histamine H₂-receptors on the parietal cell. This results in a marked $\downarrow$ in histamine-stimulated HCl secretion.
- Although other agents such as gastrin and ACh may induce acid secretion, histamine is the predominant final mediator that stimulates HCl secretion.

Therapeutic uses

- Duodenal and gastric ulcers. ✓
- Prophylaxis & treatment of stress ulcers (e.g. after burn or major trauma). ✓
- Prophylaxis against bleeding of esophageal varices. ✓
- Reflux esophagitis. ✓
- Zollinger-Ellison syndrome (gastrin-secreting tumor of the pancreas) which $\uparrow$ HCl secretion): usually larger doses are required. ✓
- With ulcerogenic drugs (e.g. NSAIDs) to protect the gastric mucosa from injury. ✓

Adverse effects (mostly with cimetidine):

- Cimetidine has anti-androgenic effects (due to block of androgen receptors) leading to $\downarrow$ sperm count, impotence and gynecomastia.
 * sprinductone + digitalis overdose
- Cimetidine inhibits hepatic microsomal enzymes (P450) leading to $\downarrow$ metabolism of other drugs e.g. theophylline, warfarin, sulphonylureas, etc.
- Reversible hepatotoxicity and Reversible anemia.
- CNS symptoms: headache, slurred speech, delirium, coma, etc. occurs mainly in elderly people with i.v. administration.
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Precautions of H₂ blockers

- Avoid sudden withdrawal to prevent rebound ulceration.
- Avoided in pregnancy and lactation (they cross the placental barrier and secreted in breast milk).
- Avoid combination of cimetidine with drugs having narrow therapeutic index (because cimetidine inhibits microsomal P450 and $\uparrow$ their toxicity).

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	Cimetidine	Ranitidine	Famotidine
H ₂ Blocking effect:	Weak	Potent	More potent
Anti-androgenic effect:	Strong	Minimal	No
Liver enzyme inhibition	Strong	Minimal	No
Adverse CNS effects:	Frequent	Less frequent	Less frequent
Duration of action:	8 h	12 h	24 h
Dose:	800 mg/day for 6-8 weeks then 400 mg/day for 6-8 months	300 mg/day for 6-8 weeks then 150 mg/day for 6-8 months	20 mg/day for 6-8 weeks then 10 mg/day for 6-8 months

3. Proton pump inhibitors (PPIs):

(Omeprazole – Lansoprazole – Pantoprazole)

Chemistry: all are imidazole derivatives.

Mechanism of action

- They are prodrugs. They are converted into the active form in the gastric mucosa and produce irreversible inhibition of gastric H⁺/K⁺ ATPase enzyme leading to ↓ both basal and stimulated HCl secretion to around the zero level for 1-2 days.
- Full restoration of acid secretion after stopping the PPI takes about 3-5 days (time of re-synthesis of H⁺/K⁺ ATPase).
- Their bioavailability is decreased significantly by food and, ideally, should be administered 1 hour before a meal.

Imidazole derivatives:

1. Nasal decongestants: Nafazoline
2. Antimicrobials: Metronidazole
3. Antifungal: Ketoconazole
4. Antiparasitic: Mebendazole
5. Proton pump inhibitors: Omeprazole

Therapeutic uses: The same as H₂ blockers

3 ulcer
2 oesophagitis
1 Zolinger Ellison

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Dose of omeprazole: 20-40 mg/day orally for 4-6 weeks then 10-20 mg/day for 4-6 months to prevent recurrence.

Adverse effects

- HCG**
- 1 - Low incidence of diarrhea, abdominal colic, dizziness, skin rash, leucopenia, and transient increase of liver enzymes.
 - 2 - Decrease vit B₁₂ absorption after more than 12 weeks of therapy due to interference with intrinsic factor secretion by the stomach.
 - 3 - Inhibition of gastric secretion leading to alteration of bioavailability of some drugs, e.g. ketoconazole, digoxin, and iron.
 - 4 - Omeprazole inhibits microsomal P₄₅₀ enzymes and decreases metabolism of phenytoin, warfarin, and cyclosporine. Pantoprazole does not affect liver enzymes.
 - 5 - Omeprazole in high dose induced gastric carcinoid tumor in rats.

Enhancing mucosal defense mechanisms

1. Sucralfate

- Sucrose*
aluminum
- It is an aluminum salt of sulfated sucrose.
 - Slightly (3%) absorbed from the GIT. The aluminum metal may accumulate in cases of renal failure, so it should be avoided in renal failure.

Mechanism of action

- It needs acidic medium to be activated. In the presence of acidic medium, it forms a complex with protein debris at the ulcer base and forms a physical barrier (so not taken with antacids, H₂ blockers, or PPIs).
- It ↓ pepsin secretion and ↑ secretion of endogenous PGs.

Adverse effects

- Constipation (due to presence of aluminum).
- ↓↓ absorption of tetracycline, digoxin and phenytoin

2. Bismuth compounds: Bismuth subsalicylate and subcitrate

Mechanism of action

- In acidic pH, it forms a complex with protein debris at the ulcer base and forms a physical barrier.

- It ↓ pepsin secretion and ↑ secretion of endogenous PGs.
- It has additional antimicrobial activity against H. pylori.

Adverse effects

- Stool and teeth discoloration.
- Encephalopathy in presence of renal failure*

Contraindications

Chronic renal failure and CNS diseases.

N.B. Both sucralfate and colloidal bismuth compound are **not given** simultaneously with antacids or H₂ blockers (at least 30 min must be elapsed in-between). Why?

need acidic medium

3. Carbenoxolone

It is a liquorice derivative having steroid structure.

Mechanism of action

- It ↑ production and viscosity of gastric mucus and ↑ mucosal resistance.
- It ↓ pepsin secretion and ↑ secretion of endogenous PGs.

Adverse effects

Salt and water retention (aldosterone-like effects) → edema and hypertension especially in cardiac and renal patients. This edema can be treated by thiazide diuretics **not by spironolactone** because both spironolactone and carbenoxolone have steroid structure and can compete with each other.

Contraindications: Hypertension and renal failure

4. Synthetic PGE₁ analogue: (Misoprostol)

Mechanism of action

- It acts on specific receptors on gastric parietal cells leading to ↓ histamine-stimulated HCl secretion.
- ↑ mucus and bicarbonate secretion (cytoprotective action)*.
- ↑ mucosal blood flow and stimulates mucosal cellular regeneration.

Therapeutic uses

Prevention of peptic ulcer in high risk patients e.g. those on long term use of NSAIDs for chronic inflammatory diseases. [misoprostol 200 µg is combined with naproxen or diclofenac in single tablet].

Adverse effects

Diarrhea and cramping pain: due to $\uparrow$ GIT motility and water secretion.
Uterine contractions during pregnancy $\rightarrow$ abortion.

Contraindications: pregnancy.

eradicated
eradicated

Eradication therapy for *H. pylori*

- Infection with *H. pylori* is the main cause of recurrence of PU.
- The following 10 days "sequential protocol" is highly effective for eradication of *H. pylori*:

PPIs

Amoxicillin 1 g

twice daily for 5 days (days 1-5).

PPIs

Clarithromycin 500 mg

Tinidazole 500 mg

twice daily for 5 days (days 6-10).

Drug therapy of bleeding peptic ulcer

- ✓ Hospitalization and complete rest.
- Fresh blood transfusion. $\square$ vit K
- Gastric lavage with ice-cold saline.
- ✓ Ranitidine: 50 mg i.v. or omeprazole 80 mg i.v. then given orally after stoppage of bleeding.
- Vitamin K₁: 10-30 mg i.m. or slowly i.v.
- * Endoscopic therapy:
 - Epinephrine injection.
 - Endoscopic clipping. $\mathcal{B}$
 - Argon laser thermal coagulation. $\mathcal{B}$

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Treatment of gastroesophageal reflux disease (GERD)

Definition: mucosal damage due to retrograde flow of gastric contents into the esophagus due to incompetent lower esophageal sphincter (LES). Heartburn is the most common complain.

Management

Non-drug therapy = life style modification

- Sleeping on a high pillow: because most damage to the esophagus occurs at night when HCl can remain in contact with the mucosa of the esophagus for long period.
- Weight reduction.
- Avoid:
 - Stress, Smoking, Spices.
 - Ulcerogenic drugs e.g. NSAIDs. ✓

Drugs ↑ LES pressure:	
▪	Bethanicol
▪	Metoclopramide
▪	Domperidone
▪	Erythromycin
Drugs ↓ LES pressure:	
▪	Anticholinergic drugs
▪	Nitrates

Drug therapy

- Prokinetic drugs. → ↑ LES pre
↑ Gastric motility
- Antacids and antacid combinations: (Gaviscon).
- Decreasing HCl secretion: (H₂ blockers and proton pump inhibitors).

Surgical treatment: if medical therapy failed.

Prokinetic drugs

Definition: they are drugs that increase upper GIT motility and increase LES pressure without causing diarrhea. They include:

- M3 receptor agonists (cholinomimetics): e.g. Bethanicol (see ANS). ✓
- Dopaminergic blockers: e.g. Metoclopramide and Domperidone.

Metoclopramide

Mechanism and pharmacological effects

- Metoclopramide ↑ lower esophageal tone, and enhances gastric emptying and upper GIT motility through:

Blocking of dopamine (D) receptors (central & peripheral) leading to decrease the inhibitory action of dopamine on the GIT motility.
Enhances cholinergic transmission in the GIT.

Antiemetic action: due to blockade of D receptors in the CTZ.

Therapeutic uses

- Gastroesophageal reflux: to enhance gastric emptying and $\uparrow$ LES pressure.
- Disorders of gastric emptying: e.g. diabetic gastroparesis and postoperative gastric retention.
- Before small bowel endoscopy (20 mg given by slow i.v.i.): to enhance gastric evacuation and peristaltic movement. Also to prevent vomiting.
- Before emergency surgery and labor (to evacuate the stomach and prevent aspiration of gastric contents).
- Treatment of nausea and vomiting of various causes.

Adverse effects

- Sedation (the most common).
- Extrapyramidal effects (dystonia and dyskinesia): due to blockade of D_2 in the basal ganglia.
- Hyperprolactinemia due to blockade of D_2 in the pituitary gland.

Drug interactions

- Anticholinergic drugs (e.g. atropine) antagonize its prokinetic action.
- Other dopamine antagonists (^{schizophrenia} antipsychotic drugs) administered with metoclopramide may precipitate acute extrapyramidal reactions.

Domperidone

Mechanism and pharmacological effects

- It blocks peripheral D_2 receptors (because it does NOT cross BBB) leading to:
 - Decrease the inhibitory action of dopamine on the GIT motility.
 - No CNS side effects. *
- Antiemetic effect less than metoclopramide.

N.B.

The CRTZ lies outside the BBB so domperidone acts as antiemetic with few CNS side effects.

Therapeutic uses

- The same uses as metoclopramide.

- To counteract nausea and vomiting caused by levodopa and bromocriptine during treatment of Parkinson's disease:
 - Because it can block D receptors in the vomiting center responsible for vomiting but not those in the basal ganglia responsible for parkinsonism.
 - Metoclopramide could not be used for this indication. Why?

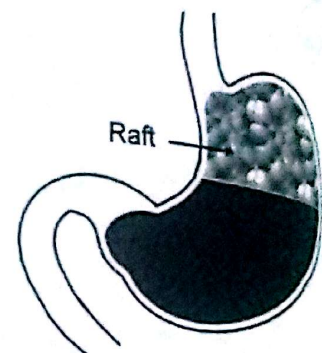
Adverse effects: there is growing evidence that domperidone may ↑ QT interval and predispose to serious arrhythmia and sudden death.

	Metoclopramide	Domperidone
Dopamine receptor blockade	Central and peripheral	Peripheral only
Extra-pyramidal side effects	Present	No
Antiemetic effect	Strong	Weaker
Cholinergic transmission	⊗ Increase	No effect

Antacids and antacid-alginate acid products

Gaviscon: (alginic acid) + Mg-trisilicate + Al-hydroxide + NaHCO_3

Alginic acid in presence of saliva and NaHCO_3 forms a highly viscous foamy solution of Na-alginate that floats on the gastric contents as a raft and prevents gastric reflux.



H2 blockers and PPIs

- PPIs are more effective than H2 blockers for the treatment of GERD.
- Once-daily dosing of PPIs provides effective symptom relief and tissue healing in 85-90% of patients; up to 15% of patients require twice-daily dosing.

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Part 2: Complications of Chronic Liver Disease

Portosystemic encephalopathy

Definition

Metabolic disorder of the CNS characterized by impaired consciousness due to increased blood levels of ammonia and benzodiazepines-like mediators (GABA-like transmitters). It usually occurs as a complication of advanced liver cirrhosis.

Management

Reduction of hyperammonemia

Diet:

- Restriction of proteins to decrease formation of ammonia. Stop any CNS drugs as they can cause hypokalemia.
- Vegetable protein is better tolerated than animal protein.

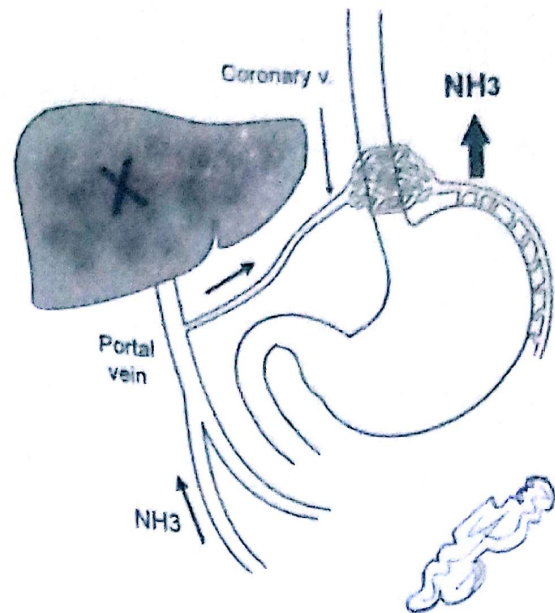
Lactulose:

- It is synthetic non-absorbable disaccharide. In the colon, it is transformed by bacteria into lactic and acetic acids to ↓ pH of the colonic contents leading to:

- Inhibition of intestinal bacteria → ↓ production of ammonia.
- ↑ transport of ammonia from blood to intestinal lumen where it is converted to the poorly absorbed ammonium ion.
- Osmotic laxation → ↑ excretion of ammonium ion.
- It is administered orally or as retention enema for patients in coma.
- Adverse effects: relatively safe drug.

Neomycin:

- It is non-absorbable aminoglycoside antibiotic.
- It ↓ blood ammonia by killing intestinal bacteria that generate ammonia.
- It is used in a dose of 1-2 gm 4 times daily orally or as retention enema.
- Small amounts of neomycin may be absorbed and result in ototoxicity and nephrotoxicity especially in patients with renal impairment.



■ Metronidazole:

- It kills anaerobic bacteria and $\downarrow$ ammonia production.
- It is the preferred option when there is fear from the side effects of neomycin.

■ Treatment of variceal bleeding due to portal hypertension

■ Management of acute bleeding

■ Fresh blood transfusion.

■ Ranitidine: 50 mg i.v. or omeprazole 80 mg i.v.

■ Drugs that decrease variceal bleeding:

■ Vasopressin (i.v.i):

- It produces mesenteric VC and $\downarrow$ portal pressure, and portal blood flow.
- It may produce systemic VC (especially in coronaries) and hypertension so they are combined with nitroglycerine to prevent coronary VC.
- The vasopressin/nitroglycerine combination is rarely used now.

■ Terlipressin:

- It is a vasopressin analogue that produces more sustained hemodynamic effects with fewer systemic side effects.

- Endoscopic sclerotherapy: injection of the varices by a sclerosing agent to obliterate it.

■ Prevention of re-bleeding (prophylaxis):

■ Beta-blockers (propranolol 40 mg twice daily). It $\downarrow$ portal BP through:

- They $\downarrow$ COP and hepatic blood flow.
- They lead to unopposed α -action in the splanchnic bed $\rightarrow$ VC $\rightarrow$ $\downarrow$ feeding of the varices.

■ H₂ blockers or proton pump inhibitors: to prevent gastroduodenal erosions.

- Metoclopramide or domperidone: to enhance gastric evacuation and $\uparrow$ LES pressure.

erosions

Part 3: Antiemetic drugs

Drug

Antiemetic mechanism

Uses as antiemetic

Adverse effects

1. Muscarinic blockers:

- Atropine ✓
- Hyoscine ✓

They block M_1 receptors in the vestibulocerebellar pathway, solitary tract nucleus, and CTZ.
 (vomiting center)

Prevention and treatment of vomiting due to motion sickness (0.3-0.6 mg/8 hrs orally).

- Blurred vision ✓
- Dry mouth ✓
- Urine retention ✓
- Glaucoma ✓
- Tachycardia ✓

2. H₁-blockers:

- Diphenhydramine ✓
- Cyproheptadine ✓
- Cyclizine ✓
- Meclizine ✓

They block H_1 (also M_1) receptors in the vestibulocerebellar pathway and CTZ.
 (vomiting center)

Vomiting due to motion sickness (diphenhydramine)
 Vomiting of pregnancy (cyclizine and meclizine)
 * True vertigo: combined with VDs to improve labyrinthine blood flow.

- Sedation (excitation may occur in children).
- Atropine-like actions (dry mouth, blurred vision, urine retention).
- Hypotension ✓

3. 5-HT₃ blockers:

- Ondansetron ✓
- Granisetron ✓
- Tropisetron ✓

They block $5HT_3$ receptors in the GIT, solitary tract nucleus and CTZ.

Vomiting due to cancer chemotherapy or radiotherapy.
 Postoperative nausea and vomiting.

Dizziness, headache, and constipation.

4. Dopamine blockers

- Metoclopramide ✓
- Domperidone ✓
- Phenothiazines e.g. chlorpromazine ✓

They block D_2 receptors in the CTZ.
 They inhibit peripheral transmission to VC.

Vomiting due to drugs or febrile illness.
 Vomiting due to cancer chemotherapy.
 Postoperative nausea and vomiting.

Sedation
 Extrapyramidal effects e.g. dystonia and dyskinesia.
 Hyperprolactinemia
 Postural hypotension ✓

Drug	Antiemetic mechanism	Uses as antiemetic	Side-effects
5. Tetrahydrocannabinol derivatives: <u>Dronabinol</u>	- It is a <u>cannabinoid receptor</u> agonist. - <u>Naloxone</u> blocks its antiemetic action	- Vomiting due to <u>cancer chemotherapy</u> - Patients <u>refractory to other</u> antiemetics.	- Sedation - Hallucinations - Psychotropic effects * <u>Postural hypotension</u> - Drug abuse
6. Vitamin B6 (pyridoxin)	May be related to the balance between <u>GABA (CNS-inhibitory transmitter)</u> and <u>glutamate (CNS excitatory transmitter)</u>.	- Vomiting in <u>pregnancy</u> (50 mg at bedtime). - Vomiting in <u>children</u>	
7. Corticosteroids ▪ <u>Dexamethasone</u> ▪ <u>Prednisolone</u>	The exact mechanism is <u>unclear</u>.	- Combined with <u>Vit B6</u> to treat vomiting in <u>pregnancy</u>.	- Hyperglycemia - Immunosuppression - Osteoporosis - Iatrogenic Cushing syndrome - Acute <u>adisonian crisis</u> if stopped suddenly - Salt and water retention
8. Benzodiazepines ▪ <u>Lorazepam</u> ▪ <u>Diazepam</u>	Allosteric facilitation of central GABA inhibitory transmission	- <u>Stress-related vomiting</u> - To control symptoms in <u>Ménière disease</u>	- Anterograde amnesia - Physical dependence - Paradoxical excitement
9. Neurokinin-1 receptor blockers: <u>Aprepitant</u>	Neurokinin 1 (NK1) receptor <u>antagonist</u>	In combination with 5-HT3 blockers to treat vomiting due to <u>cancer chemotherapy</u>	- Diarrhea and fatigue

Part 4: Antispasmodic drugs (smooth ms relaxants)

Classification

- **Anticholinergic drugs:** atropine, propantheline, oxyphenonium, hyoscine
- **Direct smooth muscle relaxants:** papaverine, mebeverine, alverine, drotaverine.
- **Mixtures:** Librax (clidinium + chlordiazepoxide), Donnatal (hyoscine + phenobarbital).

	Papaverine	Mebeverine, Alverine, Drotaverine	Librax
Chemistry & mechanism of action	It is <u>opium alkaloid</u> but chemically different from <u>morphine</u> The exact mechanism is unclear but may be due to inhibition of <u>PDE</u> enzyme $\rightarrow \uparrow$ cAMP $\rightarrow$ smooth muscle relaxation. $\uparrow$ cGMP $\rightarrow$ VD	They are <u>synthetic</u> drugs	It is a combination of: ▪ Chlordiazepoxide: benzodiazepine that has <u>antianxiety</u> effect. ▪ Clidinium: anticholinergic drug which $\downarrow$ GIT motility
Uses	▪ Spasms of the GIT, bile duct and genitourinary tract. ▪ Librax is used for treatment of <u>irritable bowel syndrome (IBS)</u>.		only intake <u>benzodiazepine</u> <u>Sym</u>
Side effects	potentially morphine ventricular tachycardia - Cardiac <u>arrhythmia</u>. - <u>Abnormal liver functions</u> in the form of $\uparrow$ serum transaminases and alkaline phosphatase. - Headache and dizziness PDE (S) PDE (H)		- Atropine-like actions e.g, dry mouth, urine retention, etc. - CNS depression: Sedation, drowsiness, confusion, etc. (Clidinium) (Chlordiazepoxide)
C/I	- Paralytic ileus. - <u>Constipation</u> for more than one week		and <u>undiagnosed abdominal pain</u>

Part 5: Constipation and Diarrhea

Therapy of constipation

Non-drug therapy

It is the first line in all cases of constipation

- Diet rich in fibers e.g. fruits, vegetables, whole meal bread, etc. to be increased to 30 g/day.
- Increase fluid intake
- Minimize tea and coffee.
- Physical exercise to activate abdominal muscles and intestinal peristalsis. This help food move more efficiently through the gut.

Drug causes of constipation:

- Atropine and related drugs.
- Aluminum containing antacids
- Adsorbents (kaolin & pectin).
- CCBs: e.g. Verapamil
- Opioids: morphine & loperamide

Drug therapy: LAXATIVES:

1. Bulk laxatives:

[Dietary fibers – Methycellulose – Bran – Agar]

Mechanism of action

They are non-digestible fibers; they retain water in the gut and distend the large intestine → activation of stretch receptors → stimulation of peristalsis.

Adverse effects: they are safe laxatives but may cause:

- Bloating and abdominal distension,
- ↓ absorption of some drugs e.g. digoxin.
- They may form masses in the gut and lead to intestinal obstruction.

2. Osmotic laxatives:

[Saline laxatives (Mg sulfate & Na salts) – Lactulose – Polyethylene glycol]

Mechanism of action

They are retained in the gut lumen and retain water by their osmotic effect → activation of stretch receptors → stimulation of peristalsis.

Adverse effects

- Saline laxatives (Mg & Na salts) may be absorbed systemically and produce hypermagnesemia and hypernatremia especially in patients with renal failure.
- Lactulose may produce abdominal discomfort.
- Polyethylene glycol may produce electrolyte disturbance.

3. Irritant (or stimulant) laxatives: → اقويط

[Castor oil – Senna – Bisacodyl]

Mechanism of action

- They produce inflammation (irritation) of the intestine and increase CAMP and inhibit Na^+/K^+ ATPase enzyme leading to:
- Accumulation of water and electrolytes in the gut lumen.
 - Direct stimulation of peristalsis by the irritant effect. distention

Adverse effects

- Castor oil
- Bad taste.
 - Stimulation of uterine contraction and abortion + Cathartic
- Senna
- It passes in urine and cause urine discoloration
 - It passes in breast milk and cause cathartic effect in the baby.
 - Prolonged use → degeneration of gut nervous plexus → atonic (cathartic) colon.
 - Increase menstrual blood flow and abortion in pregnancy.
 - Laxative dependence: Irritant laxatives cause complete evacuation of the colon. The colon requires 2-5 days before the normal fecal mass can be reestablished. The patient becomes worry regarding the lack of bowel movement during this period and may use the laxative again and a vicious cycle is established leading to partial or complete loss of normal bowel function.
- Bisacodyl
- It is prepared as enteric coated tablets to avoid gastric irritation. If it is given with milk or with other drugs that change gastric pH, the enteric coating may dissolve in the stomach and cause gastric irritation and pain
 - Prolonged use → degeneration of gut nervous plexus → atonic (cathartic) colon (should not be used more than 10 days)

4. Stool softeners: [Docusate sodium]

Mechanism: They facilitate incorporation of water into the intestinal contents and soften the fecal mass and ease its passage.

5. Lubricant laxatives:

[Liquid paraffin] - [Glycerin suppositories] - Evacuant enema

Mechanism of action

- Paraffin oil coats the fecal matter and prevents water absorption from it.
- Glycerin has hygroscopic effect. It draws water from rectal mucosa and lubricates the anal canal. It also stimulates reflex rectal contractions and promotes stool evacuation in 15-20 min.

N.B.

► Evacuant enemas:

- Solutions (small volume) of tap water (135 ml) with added mineral oil, hypertonic sorbitol, $MgSO_4$, docusate K.
- All are safe for self-administration to facilitate passage of stool in painful conditions of the anus.

Adverse effects: paraffin oil decreases absorption of fat-soluble vitamins * KEDA

6. Chloride channel activators: Lubiprostone

Mechanism of action

It acts by activating chloride channels to increase fluid secretion in the intestinal lumen. This eases the passage of stool and causes little change in electrolyte balance.

General indications of laxatives

- Constipation: laxatives should not be used for prolonged duration to avoid laxative dependence.
- To fasten excretion of toxic substances from the GIT.
- To prepare the bowel before X-ray or colonoscopy.
- Hepatic encephalopathy (lactulose) to kill ammonia producing bacteria.
- Painful anal conditions e.g. anal fissure or piles.
- Postoperative: e.g. after hemorrhoids (piles) to avoid strain.

Contraindications of laxatives

- Laxatives are dangerous in cases of undiagnosed abdominal pain or inflammatory bowel disease. They may lead to intestinal perforation.
- Organic obstruction of the GIT.

Therapy of diarrhea

Diarrhea: passage of frequent unformed stool

Causes of diarrhea

■ Infectious diarrhea:

- Bacterial: *E. coli*, *Salmonella*, *Shigella*, *V. cholera*, etc.
- Viral: enteroviruses.
- Fungal: *Candida albicans*
- Protozoal: *E. histolytica*, *Giardia*, etc.
- Helminthes: *Schistosomiasis*, intestinal parasites.

1 infectious
2 inflammatory
3 hormonal
4 drug
5 malabsorption

■ Hormonal (secretory) diarrhea: e.g. serotonin in carcinoid syndrome, calcitonin in medullary thyroid carcinoma, histamine in mastocytosis, thyroxine in hyperthyroidism.

Diarrhea is caused by: (1) increased water secretions into the intestinal contents and (2) increased intestinal motility.

■ Malabsorption syndromes: e.g. bile acid malabsorption



■ Inflammatory (exudative) diarrhea: caused by inflammatory bowel diseases e.g. Crohn's disease (transmural lesion in the small intestine) and ulcerative colitis (ulceration of the colon with bloody diarrhea).

■ Iatrogenic (drug induced) causes:

- Overuse of laxatives.
- Mg-containing antacids.
- Clindamycin → pseudomembranous colitis.
- Cholinomimetic drugs.

C. difficile BBs

malabsorption drug

Shit



Patterns of diarrhea

- Acute self-limited diarrhea: acute diarrhea disappears within 24 hrs.
- Acute diarrhea (<2 weeks): passage of watery stool more than 10 times/day associated with dehydration and electrolyte imbalance.
- Chronic diarrhea (>2 weeks): persistent diarrhea for 3 weeks in adults or 4 weeks in infants. It causes weight loss and weakness.

Investigations of diarrhea

- Stool examination:
 - Macroscopic: consistency, color, blood, parasites, etc.
 - Microscopic: RBCs, WBCs, parasites, ova, etc.
 - Stool culture and sensitivity tests.
- Endoscopy and biopsy in chronic cases.
- Radiologic examination: by barium enema.

Treatment of diarrhea

Lines of therapy

- Maintenance of fluid and electrolyte balance: is the first priority.
- Non-specific antidiarrheal agents: should be applied after exclusion of other relevant causes of diarrhea.
- Specific antidiarrheal agents: treatment of the cause e.g.
 - Antimicrobials for infectious diarrhea.
 - Antiinflammatory drugs for inflammatory bowel diseases.
- Antispasmodic drugs: if there is associated colic or abdominal cramps.

Maintenance of fluid and electrolyte balance

Oral Rehydration Therapy (ORT):

- Balanced salt solution containing electrolytes and glucose (glucose is important for sodium and consequently water absorption).
- 90% of acute cases of childhood diarrhea can be corrected using ORT only.

- Intravenous solutions: in severe dehydration.

N.B. in infants with dehydration, blood pH, serum Na⁺ and K⁺ must be measured before giving any i.v. solution to avoid electrolyte and acid/base imbalance.

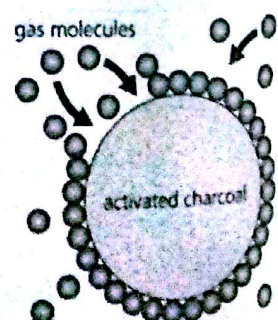
Non-specific antidiarrheal therapy

1. Adsorbents (Kaolin, pectin, activated charcoal)

Mechanism

- They adsorb water, microorganisms and toxins.
- They coat the mucosa and protect it.

Side effects: they may ↓ absorption of other drugs.



2. Bismuth subsalicylate

Mechanism

- ① Bismuth: provides a protective coat for the mucosa and binds toxins produced by *V. cholera* and *E. coli*.
- ① Subsalicylate: hydrolyzed by intestinal bacteria into salicylic acid → ↓ synthesis of PGs responsible for intestinal inflammation, hypermotility and secretions.

Uses: treatment and prophylaxis of traveller's diarrhea. *

3. Anti-cholinergic drugs: (Atropine, hyoscine and propantheline)

Mechanism

- ✓ Antidiarrheal action: ↓ colonic peristalsis by blocking the response of intestinal smooth muscle to cholinergic stimulation.
- ✓ Antispasmodic action: relieve cramps associated with diarrhea. ✓

4. Opiates and opioid preparations:

- Natural opiates: opium tincture
- Synthetic opioids: diphenoxylate and loperamide

Mechanism

- They act on opioid μ (mu) receptors enteric nervous system (ENS) leading to ↑ segmenting (non-propulsive) contractions of the intestine and increase resistance to flow through the lumen. ↓
- They act on opioid δ (delta) receptors in the ENS leading to ↑ water absorption and ↓ water secretion.
- They act on presynaptic opioid receptors in the ENS leading to ↓ Ach release.

Diphenoxylate and loperamide

- They are synthetic derivative of meperidine.
- Loperamide cannot cross BBB but diphenoxylate can cross BBB poorly (no CNS effects in usual therapeutic doses) but it can cause addiction if used in large doses and for prolonged duration.
- They are commonly combined with atropine (e.g. Lomotil) is a combination of diphenoxylate 2.5 mg + atropine 0.25 mg) to produce more ↓↓ in intestinal motility and decrease liability for abuse.

Side effects

- Anti-cholinergic side effects.
- Addiction if used for prolonged duration.
- * Precipitation of toxic megacolon if used in ulcerative colitis.

5. Cholestyramine

Mechanism: it binds bile acids in the intestine preventing their absorption and decreasing their irritation.

Uses:

- Chronic diarrhea caused by bile salt malabsorption.
- ✓ Treatment of pseudomembranous colitis (see chemotherapy).

+ digitalis toxicity

hypercholesterinaemia

Specific anti-infective agents

- It is not necessary in simple gastroenteritis as most cases are viral in origin.
- Chemotherapy is necessary in specific types of enteritis e.g.
 - Shigella: ampicillin 1gm/6hrs or tetracycline 250 mg/6hrs for 5 days.
 - Salmonella: chloramphenicol 3 gm/d or ciprofloxacin 500 mg/12hrs for 10 days.
 - V. cholera: tetracycline 500 mg/6hrs for 5 days.
 - E. coli: tetracycline 500 mg/6hrs for 3 days.
 - Staph aureus: flucloxacillin or vancomycin 500 mg/6hrs for 5 days.
 - Ciprofloxacin 500 mg/12hr for 5 days could be used for most cases of bacterial diarrhea.

Anti-inflammatory drugs: → inflammatory bowel

1. Sulfasalazine (5-aminosalicylic acid "5-ASA" + sulfapyridine)

Mechanism: In the colon, the "azo" bond is broken by bact flora to release 5-ASA and sulfapyridine:

- ✓ 5-ASA: has anti-inflammatory (↓ PGs and LTs), immunosuppressive, and free radical scavenging action
- ✓ Sulfapyridine: is sulfonamide having antibacterial action

Uses:

Active ulcerative colitis (3-4 gm/day) and to maintain remission (2 gm/day).
Rheumatoid arthritis.

Side effects: mainly (due to sulfapyridine) (sulfonamide) → drug allergy, bone marrow depression and megaloblastic anemia (avoided by giving folic acid). * inhibit

Other aminosalicylates:

- Mesalazine: modified-release preparation.
- Olsalazine is a dimer of 5-ASA. It is cleaved in the lower bowel to release 5-ASA.

2. Corticosteroids

Mechanism *induction of therapy not maintenance*

- Stimulation of Na^+ absorption from the intestine.
- Anti-inflammatory action (see endocrine).

Uses: they are given orally or as enema in severe cases.

- To control acute episodes of Inflammatory bowel diseases
- Refractory diarrhea unresponsive to other agents.

Travellers' diarrhea:

- Diarrhea that occurs to travellers and tourists in high endemic areas. Transmission of infection is done through contaminated food or water.
- **Drug therapy:**
 1. Prophylaxis: doxycycline (100 mg/day orally)
 2. Treatment: doxycycline + bismuth subsalicylate + fluids

3. Immunosuppressive agents

- Cytotoxic drugs (azathioprine and 6-mercaptopurine): can be used in ulcerative colitis and Crohn's disease in small dose to avoid bone marrow depression.
- Cyclosporine-A use is limited for severe cases due to its toxicity on chronic use.

Notes

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N.B.

- Metronidazole may be used in Crohn's disease to eradicate anaerobic bacteria.
- Infliximab (monoclonal antibodies): can be used in Crohn's disease to ↓ TNF α .
- Aspirin and indomethacin may of value in acute diarrhea because they ↓ PGs synthesis → ↑ absorption and ↓ secretions of intestinal fluids.
- Clonidine (α_2 stimulant) can be used in diabetic diarrhea to ↑ intestinal water absorption and ↓ electrolyte secretion.
- Alosetron: 5HT $_2$ antagonist that blocks receptors on enteric neurons thereby can reduce colonic motility. It is used for treatment of irritable bowel syndrome with diarrhea.
- Tegaserod: 5HT $_4$ partial agonist that result in stimulation of peristalsis. It is used for treatment of irritable bowel syndrome with constipation.

Part 6: Drug therapy of gallstones (cholelithiasis)

Choleretics: are agents that increase bile production e.g. bile acids and bile salts.

Hydrocholeretics: are agents that increase volume of bile e.g. dehydrocholic acid.

Cholagogues: are agents that stimulate the evacuation of gall bladder e.g. olive oil.

The following drugs are used to dissolve non-calcified cholesterol stones.

Chenodeoxycholic acid (CDCA): It ↓ hepatic cholesterol synthesis and ↑ bile acid and phospholipid synthesis.

Ursodeoxycholic acid (UDCA)

It is a metabolite of chenodeoxycholic acid.

- It is more potent in reduction of hepatic cholesterol synthesis without affecting the endogenous bile acid synthesis.
- Both CDCA and UDCA are given orally in a dose of 10-15 mg/kg/day for 6-12 month.
- Diarrhea is common side effect with CDCA but is unusual with UDCA.

Notes

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